

REQUEST FOR CONTINUED EXAMINATION (RCE) TRANSMITTAL

Subsection (b) of 35 U.S.C. § 132, effective on May 29, 2000 provides for continued examination of a utility or plant application filed on or after June 8, 1995.

See The American Inventors Protection Act of 1999 (AIPA)

Application Number: 09/642,160

Filing Date: August 21, 2000

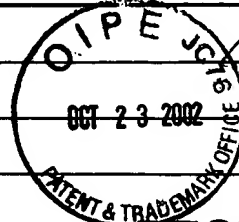
First Named Inventor: Bent Hojgaard

Group Art Unit: 1615

Examiner: T. Ware

Attorney Docket Number: 06063.0019

Attorney Customer Number: 22,852



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This is a Request for Continued Examination (RCE) under 37 C.F.R. § 1.114 of the above-identified application.

Note: 37 C.F.R. § 1.114 is effective on May 29, 2000. If the above-identified application was filed prior to May 29, 2000, applicant may wish to consider filing a continued prosecution application (CPA) under 37 C.F.R. § 1.53(d) instead of a RCE to be eligible for patent term adjustment provisions of the AIPA. See "Changes to Application Examination and Provisional Application Practice," Interim Rule, 65 Fed. Reg. 14865 (March 20, 2000). Off. Gaz. Pat. Office 47 (April 11, 2000), which established RCE practice.

1. Submission required under 37 C.F.R. § 1.114:

a. ☒ Previously submitted

- i. ☒ Consider the amendment(s)/reply after final under 37 C.F.R. § 1.116 previously filed on July 1, 2002.
- ii. ☐ Consider the arguments in the Appeal Brief of Reply Brief previously filed on [Date].
- iii. ☐ Other _____

b. ☒ Enclosed:

- i. ☒ Amendment/Reply
- ii. ☐ Affidavit(s)/Declaration(s)
- iii. ☐ Information Disclosure Statement
- iv. ☐ Other _____

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2. Miscellaneous

- a. ☐ Suspension of action on the above-mentioned application is requested under 37 C.F.R. § 1.103(c) for a period of [number] months. (Period of suspension shall not exceed 3 months; fee under 37 C.F.R. § 1.17(i) required.)
- b. ☐ Other _____

3. Fees

a. ☒ The filing fee is calculated as follows:

- i. ☒ \$740.00 RCE fee required under 37 C.F.R. § 1.17(e)
- ii. ☒ Petition for extension of time for (one Month) \$110.00
- iii. ☐ Other _____

b. ☒ Checks in the amount of \$740.00 and \$110.00 are enclosed.

c. ☒ The Commissioner is authorized to charge any deficiencies in the filing fees, or credit any overpayments to Deposit Account No. 06-0916.

Signature of Applicant, Attorney, or Agent Required

Name: Matthew T. Latimer

Reg. No.: 44,024

Signature: *Matthew T. Latimer*

Date: October 23, 2002

Certificate of Mailing or Transmission

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PATENT

Attorney Docket No. 06063.0019

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:)

Bent HOJGAARD et al.)

Application No.: 09/642,160)

Filed: August 21, 2000)

Group Art Unit: 1615)

Examiner: T. WARE)

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OCT 25 2002

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For: A PHARMACEUTICAL DELIVERY SYSTEM FOR VITAMIN C AND VITAMIN E
AND USE OF A COMBINATION OF VITAMIN C AND E FOR PREVENTING OR
TREATING CONDITIONS INVOLVING OXIDATIVE STRESS

Assistant Commissioner for Patents
Washington, D.C. 20231

RESPONSE TO FINAL OFFICE ACTION

Sir:

In response to the Final Office Action mailed February 26, 2002, continued prosecution of this application being permitted by the Request for Continued Examination filed herewith, Applicants respectfully request reconsideration and withdrawal of the rejections set forth in the Final Office Action in view of the following remarks and those of the previous responses. Claims 38-73 are pending and under examination in this application.

I. *Priority*

The Office indicates that a certified copy of the priority document, Danish Patent Application No. 1999 01145, filed on August 20, 1999, has not yet been submitted. Attached to the Request for Reconsideration After Final Rejection filed July 1, 2002, was a certified copy of the priority application. The Request for Continued Examination filed herewith directs the

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Office to enter the Request for Reconsideration of July 1, 2002. In view of the submitted priority document, Applicants respectfully submit that their claim for priority is now perfected.

II. *Maintained Rejections*

In the Final Office Action, the Office maintains the rejection of claims 38-56 under 35 U.S.C. § 103(a) as unpatentable over Valducci ("the '703 patent"), and claims 57-73 over the '703 patent in view of Sato *et al.* (1993) or Niki (1986). Applicants respectfully traverse these rejections and submit that the present claims are patentable over the cited references, alone or in combination.

Claims 38, 57, and 67 are the only independent claims that are currently pending. Because dependent claims include all of the elements recited in the claims from which they depend, if an independent claim is patentable over a reference or combination of references, all claims that depend from it will likewise be patentable over that reference or those references. Accordingly, Applicants will address the outstanding rejections as they apply to the independent claims only, with the understanding that the arguments are equally applicable to all of the claims that depend from them. Because independent claims 38, 57, and 67 are patentable over the cited references (as discussed below), dependent claims 39-56, 58-66, and 68-73 are patentable as well, and for the same reasons.

A. The '703 Patent

The Office for the first time specifically identifies Example 10 of the '703 patent as disclosing a composition comprising both vitamin C and vitamin E. (Final Office Action at page 2.) The Office asserts that the composition renders present claim 38 obvious. Applicants

respectfully traverse this rejection and submit that the '703 patent does not render claim 38 obvious.

The Office notes that, in the composition of Example 10 of the '703 patent, vitamin C is present in an amount within the range recited in present claim 38. The Office recognizes that the composition of Example 10, while comprising vitamin E, does not comprise vitamin E in an amount within the range recited in present claim 38 (*i.e.*, an amount in the delivery system so as to deliver a daily dose corresponding to 50 mg - 500 mg of α -tocopherol). The Office also recognizes that the '703 patent does not provide any motivation to increase the amount of vitamin C or vitamin E provided in the composition of Example 10.¹ However, the Office asserts that it "would be within the ken of one skilled in the art . . . to provide greater doses of vitamins . . . in someone who is malnourished." (Final Office Action at pages 2-3.) Applicants respectfully submit that the motivation provided by the Office is insufficient to motivate one to select the presently claimed range of vitamin E.

Present claim 38 recites a pharmaceutical delivery system for oral delivery of the antioxidants vitamin C and vitamin E **to obtain a controlled ratio between vitamin C and vitamin E** in blood plasma in humans or animals. The controlled ratio recited in claim 38 is a daily dose corresponding to 60 mg - 2 g of vitamin C, and an amount of vitamin E corresponding to 50 mg - 500 mg of α -tocopherol. The specification states that the present invention is based on the notion that a certain ratio between vitamin C and vitamin E is necessary for optimum

¹ Applicants respectfully submit that, contrary to the assertion of the Office on page 3 of the Final Office Action, under the heading "Response to Arguments", Applicants have not argued that the '703 patent provides a motivation to increase the amounts of either vitamin C or vitamin E provided in the '703 patent.

protection of LDL particles. (See the present specification at page 7, lines 22-24, for example.) Accordingly, in order to render obvious present claim 38, the prior art must recognize the importance of the controlled ratio. See MPEP § 2144.05. Applicants respectfully submit that the art cited by the Office does not recognize this importance.

It is not sufficient for the Office to simply assert that one would have been motivated to increase the amount of vitamin E in the composition of Example 10. Rather, the Office must show that one would have been motivated to increase the amount of vitamin E from the disclosed amount to an amount within the range recited in claim 38. Applicants respectfully submit that the Office has not shown such a motivation.

In the absence of a showing of motivation to achieve the presently claimed ranges, the Office has failed to set forth a *prima facie* case of obviousness. Therefore, Applicants respectfully request that the Office reconsider and withdraw the rejection of claim 38 under 35 U.S.C. § 103(a) as unpatentable over the '703 patent.

B. The '703 Patent in View of Sato *et al.* (1993)

The Office maintains its rejection of claims 57 and 67 over the '703 patent in view of Sato *et al.* The Office relies on the '703 patent for the disclosure discussed above. The Office relies on Sato *et al.* for the disclosure that vitamin A [*sic*, E] and vitamin C interact synergistically to decrease oxygen toxicity in oxidative stress situations. Based on these disclosures, the Office asserts that it would have been obvious to one of ordinary skill in the art to treat oxidative stress with the composition of Example 10 of the '703 patent, as modified by the Office to comprise "greater doses of vitamins", "with the motivation of maintaining high concentrations of vitamins C and E". (Final Office Action at page 4.) Applicants respectfully traverse this rejection.

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Present claim 57 recites a method of treating oxidative stress disorders and associated diseases and conditions, comprising administering to an individual a combination of vitamin C and vitamin E in sufficient amounts to achieve a concentration of vitamin E in the blood plasma that is at least 20 $\mu\text{mol/liter}$ and a concentration of vitamin C in the blood plasma that is at least 40 $\mu\text{mol/liter}$, and to a ratio of approximately 1:1 to 3:1, in not more than 8 weeks from the first administration. Claim 67 recites a method of treating oxidative stress disorders and associated diseases and conditions comprising administering to an individual at least one dosage unit per day of a combination of vitamin C and vitamin E in sufficient amounts to raise the concentration of the vitamins in blood plasma sufficiently to treat at least one oxidative stress disorder and to a controlled ratio. The method further recites, among other things, that the method achieves a concentration of vitamin E in the blood plasma of at least 20 $\mu\text{mol/liter}$, and a concentration of vitamin C in the blood plasma of at least 40 $\mu\text{mol/liter}$.

Initially, as discussed above, the '703 patent provides no motivation to adjust the concentrations of vitamin C or vitamin E provided in the composition of Example 10 of the '703 patent, for whatever purpose. Furthermore, the general motivation provided by the Office to increase the amount of vitamin E in the composition of Example 10 to maintain "high concentrations of vitamins C and E" is contradicted by the disclosure of Sato *et al.*, which is specifically relied upon by the Office to assert that claims 57 and 67 are obvious.

Sato *et al.* discloses that combinations of α -tocopherol (vitamin E) and vitamin C were effective at improving neuronal survival under oxidative stress. Sato *et al.* discloses that concentrations of 10^{-8} to 10^{-6} (*i.e.*, 10 nM - 1 μM) of vitamin E and 2×10^{-6} (*i.e.*, 2 μM) vitamin C were more effective than either vitamin alone. (Sato *et al.* at page 1179.) Applicants respectfully

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submit that neither of these concentrations are within the concentration ranges recited in present claims 57 and 67. Indeed, they are each at least 20 times less than the minimum amounts recited in present claims 57 and 67. Furthermore, Sato *et al.* discloses that use of vitamin C at 200 μ M is toxic. (Sato *et al.* at page 1182.)

In essence, the Office has asserted that it would have been obvious to increase the amounts of vitamins C and E disclosed in Example 10 of the '703 patent, and supported that assertion with a disclosure that suggests that, to treat oxidative stress, one should use concentrations of vitamins C and E that are less than the amounts present in the composition of Example 10. Applicants respectfully submit that Sato *et al.* fails to support the Office's assertion that it would have been obvious to increase the amount of vitamin E and/or vitamin C in the composition of Example 10 of the '703 patent. Rather, Applicants submit that, had one looked to the disclosure of Sato *et al.* in an effort to obtain guidance on modifying the composition of Example 10 of the '703 patent so that it would be suitable for treating oxidative stress, that person would have been motivated to decrease the amounts of vitamins C and E. In other words, Applicants submit that Sato *et al.* teaches away from increasing the amounts of vitamins C and E in the composition of Example 10 of the '703 patent.

Because the combined teachings of the '703 patent and Sato *et al.* teach away from the methods of present claims 57 and 67, Applicants respectfully submit that the motivation provided by the Office for increasing the concentrations of vitamins C and E in the composition of Example 10 of the '703 patent is not supported by the cited references. Thus, the Office has failed to set forth a *prima facie* case of obviousness of claims 57 and 67. Accordingly,

Applicants respectfully request that the Office reconsider and withdraw the rejection of claims 57 and 67 under 35 U.S.C. § 103(a) over the '703 patent in view of Sato *et al.*

C. The '703 Patent in View of Niki (1986)

The Office maintains its rejection of claims 57 and 67 over the '703 patent in view of Niki. The Office relies on the '703 patent for the disclosure discussed above. The Office relies on Niki for the disclosure that vitamin A [*sic*, E] and vitamin C interact synergistically to decrease oxygen toxicity, and thus the occurrence of various diseases and disorders. Based on these disclosures, the Office asserts that it would have been obvious to one of ordinary skill in the art to treat oxidative stress with the composition of Example 10 of the '703 patent, as modified by the Office to comprise "greater doses of vitamins", "with the motivation of maintaining high concentrations of vitamins C and E". (Final Office Action at page 4.) Applicants respectfully traverse this rejection.

Present claims 57 and 67 have been discussed above, as has the disclosure of the '703 patent.

Niki reviews the state of the art in 1986 with respect to interactions between vitamins C and E. Niki summarizes data showing that vitamins C and E can interact to inhibit oxidation. However, Niki provides no data relating to amounts of vitamins C and E to use to treat oxidative stress and disorders and diseases associated with oxidative stress. In other words, Niki neither discloses nor suggests appropriate amounts of vitamins C and E for treating oxidative stress or diseases or disorders associated with oxidative stress. Thus, even if one were to look to the disclosure of Niki in an effort to obtain guidance on modifying the composition of Example 10 of the '703 patent so that it would be suitable for treating oxidative stress and/or disease or disorders

associated with oxidative stress, that person would have found no disclosure or suggestion to help him in his efforts.

As discussed above, the '703 patent provides no motivation to alter the amounts of vitamins C and E in the composition of its Example 10. Moreover, the '703 patent provides no motivation to alter the amounts of vitamins C and E in the composition of its Example 10 to achieve the controlled ratio and plasma concentration recited in present claims 57 and 67, and disclosed on page 7, lines 22-24 of the present specification. The specification states that the present invention is based on the notion that a certain ratio between vitamin C and vitamin E is necessary for optimum protection of LDL particles. (See the present specification at page 7, lines 22-24, for example.) Accordingly, in order to render obvious present claims 57 and 67, the prior art must recognize the importance of the ^{not in claim → only ratio, not stated ratio} controlled ratio. See MPEP § 2144.05. Applicants respectfully submit that neither the '703 patent nor Niki recognizes this importance.

In accordance with the discussion above with regard to the '703 patent, in order to set forth a proper *prima facie* case of obviousness of claims 57 and 67, the Office must show that one would have been motivated to increase the amount of vitamin E from amount disclosed in Example 10 of the '703 patent to an amount within the range recited in claims 57 and 67. Applicants respectfully submit that the Office has not shown such a motivation.

In the absence of a showing of motivation to achieve the concentration ranges of vitamins C and E recited in the present claims, the Office has failed to set forth a *prima facie* case of obviousness. Therefore, Applicants respectfully request that the Office reconsider and withdraw the rejection of claims 57 and 67 under 35 U.S.C. § 103(a) as unpatentable over the '703 patent in view of Niki.

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Furthermore, even if one of ordinary skill in the art had found motivation to adjust the amounts of vitamin C or E disclosed in the '703 patent based on the disclosure of Niki, that person still would not have achieved the invention of present claims 57 and 67. More specifically, Niki teaches the protective effect of vitamin C on vitamin E. Niki ascribes the protective effect to the ability of vitamin C to regenerate vitamin E. (See Niki at page 195, first full paragraph, for example.) Thus, if Niki teaches anything at all about preparing a composition comprising both vitamin C and vitamin E, it teaches that, to achieve an equivalent effective amount of vitamin E, a composition comprising both vitamin C and vitamin E may have less vitamin E than the amount needed if vitamin E were to be supplied without vitamin C.

Applicants respectfully submit that, even if one were to attempt to modify the concentration of vitamin E disclosed in the '703 patent based on the disclosure of Niki, that person would lower the amount of vitamin E provided. Because the amount of vitamin E disclosed in the '703 patent is less than the amount recited in present claims 57 and 67, modifying the '703 patent based on the disclosure of Niki would result in a composition that is even less like the composition used in the methods of present claims 57 and 67 than the composition disclosed in the '703 patent. Therefore, even if one were to have somehow found motivation to combine the '703 patent and Niki, the resulting combination would not render present claims 57 and 67 obvious. For at least this reason, Applicants respectfully submit that the Office has failed to set forth a *prima facie* case of obviousness of claims 57 and 67 over the '703 patent in view of Niki. Thus, for at least this reason, Applicants respectfully request that the Office reconsider and withdraw the rejection of claims 57 and 67 over the '703 patent in view of Niki.

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III. *Response to Advisory Action*

In an Advisory Action dated August 19, 2002, the Office asserts that arguments substantially identical to those presented above were insufficient to place the claims in condition for allowance because: 1) not all claims recite a ratio of vitamin C to vitamin E; 2) administration of the doses recited in the claims would have been obvious in view of the '703 patent; and 3) the scope of the claims is not within the scope of evidence provided by the specification at page 7. (Advisory Action at page 2.) Applicants respectfully traverse these assertions.

First, Applicants respectfully submit that all of independent claims 38, 57, and 67 clearly recite a ratio of vitamin C to vitamin E: a daily dose of 60 mg - 2 g of vitamin C and enough vitamin E to achieve a level of 50 mg - 500 mg α -tocopherol.

Second, the non-obviousness of the claims in view of the '703 patent, alone or in combination with Sato *et al.* or Niki, is discussed in detail above.

Third, the scope of the claims is within the scope of evidence provided by the specification. The specification discloses that a ratio of concentrations between vitamin C and vitamin E in the blood plasma from 1:5 to 5:1 can be achieved according to the invention. (See the present specification at page 7, lines 26-29, for example.) The ratio is achieved by at least once daily oral administration of the delivery system of the invention. (See the present specification at page 7, lines 31-34, for example.) The daily dose of each of the vitamins corresponds to 60 mg - 2 g of vitamin C and, preferably, 50 mg - 500 mg of α -tocopherol. (See the present specification at page 9, lines 15-23, for example.) Accordingly, the scope of the claims is within the scope of evidence provided by the specification.

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IV. *Conclusion*

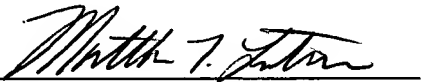
For at least the reasons set forth above, in addition to the arguments previously submitted during the prosecution of this application, Applicants submit that the cited references, alone or in combination, fail to render the presently claimed invention obvious. Thus, Applicants respectfully request reconsideration and withdrawal of the rejections of claims 38-73, and allowance of this application.

If the Office believes anything further is necessary in order to place this application in even better condition for allowance, Applicants request that their undersigned representative be contacted at the telephone number or e-mail address below to discuss the remaining issues.

Please grant any extensions of time required to enter this Request, and charge any additional required fees to our Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

By: 

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Date: October 23, 2002

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